Review of answers from experts to EMEA questions

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Design of the studies

- **Controversial issue**
- Withdrawal design:
  - Carry over of positive effect
  - Bias a favourable outcome
  - Placebo control unethical
  - More difficult to treat after every flare
  - Definition of flare, validation
- Active comparator controlled study:
  - Not feasable
  - Not supported by industry

Outcome measures for JIA

- Threshold of response to be increased
  - Clinical remission as an endpoint (in phase IV studies?)
  - Longer duration of studies?
- New endpoints
  - Composite DAS, minimal disease activity, effectiveness, joint erosion, fatigue, growth, pubertal maturity…
- SOJIA – criteria (fever!)
- Uveitis!
- Revise ACR criteria
  - CHAQ, LOM, PGA…
  - Pain?

Outcome predictors

- No controversy
- “Absolutely vital”
- What we understand under “outcome predictors”
- Legal basis for requesting “basic research” endpoints and biobanking?

B-cell depletion in JIA

- Studies recommended
- Need in patients after (several) anti-TNF failure
  - Studies on anti-TNF switching needed
- Population small (estimate <1 – 20%)
- Safety issues
  - infection (PML)
  - malignancy (risk relativised by current anti-TNF warnings)
- Maybe more needed in other conditions, safety to be extrapolated afterwards

Registry

- Consensus on need
- Experience from national registries
  - danger of bias if sponsored by industry
  - data quality and monitoring
  - definition of data set
  - patient identification issues (data protection, transition)
- Funding
- Current initiatives

Extrapolation

- Controversial issue
- PK studies?
- Possible (no studies needed) in adolescents, especially in RF+ Poly
- No extrapolation of safety (but lessons to be learned from RA)
- Extrapolation of safety and efficacy from polyarticular course to other forms (?)
- Extrapolation within class?

Classification of JIA

- Discovering the pathway of pathomechanism?
  - We are not there
  - Will not help in classification – evolves during disease course
  - Definitely will help. Already heterogeneity of SOJIA unraveled (response to anti-IL1)
  - International collaborative studies should focus on
  - Rather response to previous drug
  - Tailored therapy – not so far future

Classification of JIA

- "Polyarticular course"
  - Lumps many different pathologies together
  - Practical concept for now;
  - specially for sponsors
  - but for future?
  - Includes 4 subtypes of JIA (not PsA, ERA)

- Persistent oligoarthritis
  - Need for definition – if does not respond to i.a. steroid therapy (frequent relapses with radilogicalprogression)
  - Can be treated with biologics (cca 1%)
  - But not suitable for inclusion to trials?
  - Represents same disease as RF negative polyarthritis?

ERA and PsA

- Should be studied separately
- Can be included in one studies with other subtypes
- Respond to same treatment
- Feasability of separate studies
- Classification issues with PsA
- ACR criteria not suitable for ERA

Early, persistent and systemic arthritis

- Superficially attractive, but needs definition
- Different than in adults
- Evolution different in different subtypes
- Reflects rather aggressivity of previous treatments than biologic nature
- Suitable but clinical subtypes need to be included

Systemic JIA

- Can/cannot be divided to two distinct subforms
- With and without systemic features
- Responsive/nonresponsive to anti-IL1 treatment
- Active comparator not available, head to head studies not feasible

Age groups

- 2 years up regardless type
- ERA from 2, 6, 8, 12 years
- Focus on younger ages
- Depend on mechanism of action
  - B cell depletion after completion of immunisation

Uveitis

- Consensus: studies needed
- Should not be exclusion criterion
- Lack of validated outcome measures
- Studies must not delay approval for treatment of arthritis

Lupus/ SLE nephritis

- Should/should not be studied separately
- Lack of validated score for SLE severity
- Further work needed for outcome measures
- Standard of care – cyclophosphamide vs. MMF
- B-cell depletion?
- Withdrawal design not appropriate
- No suitable outcome predictors

Other diseases

- Studies ongoing in JDM, autoinflammatory diseases
- Low number of patients with scleroderma, vasculitides
  - Inclusion to adult studies